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10/691,012	10/22/2003	Ole Buchardt	ISIS-5299	5682

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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
11/06/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/691,012	BUCHARDT ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-36,38-41,43-45 and 47-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-36,38-41,43-45 and 47-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Response filed 08/06/2008 is acknowledged. There is no change in claim status. Claims 34-36,38-41,43-45,47-73 are pending.

2. Applicant's arguments have been considered but are and not deemed persuasive. The following rejections constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112, first paragraph (enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 34-36,38-41,43-45,47-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for extra-cellular administration of the oligomers from the broad genus of a “polyamide nucleic acid oligomer containing neutral amide backbone linkages”, does not reasonably provide

enablement for *in vivo* extracellular administration that produces an intracellular biological response (such as modulation of protein expression). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Specification describes inhibition of transcription by peptide nucleic acids (PNAs) *in vitro* (Example 68), and inhibition of expression of E2 mRNA of papillomavirus *in vitro.* There are no examples of *in vivo administration as claimed and of* effect thereof.

The assertion of the alleged *in vivo* effect stems from observation that the oligomers used in the method

> …are able to recognize duplex DNA by displacing one strand, thereby presumably generating a double helix with the other one. Reagents which recognize 17-18 bases are of particular interest since this is the length of unique sequences in the human genome. The compounds of the invention also should be able to form triple helices with dsDNA.
>
> Whereas the improved binding of the compounds of the invention should render them efficient as antisense agents, it is expected that an extended range of related reagents may cause strand displacement, now that this surprising and unexpected new behavior of dsDNA has been discovered.

Paragraphs [0056]-[0057].

Based on this alleged (emphasis added in the quotation above) effect, specification states that the method is applicable to *in vivo* treatment:

> [0058] Thus, in one aspect, the present invention provides methods for inhibiting the expression of particular genes in the cells of an organism, comprising administering to said organism a reagent as defined above which binds specifically to sequences of said genes.
>
> [0059] Further, the invention provides methods for inhibiting transcription and/or replication of particular genes or for inducing degradation of particular regions of double stranded DNA in cells of an organism by administering to said organism a reagent as defined above.

However, there is no demonstration that PNAs administered in vivo will be capable to exert the same effect as observed *in vitro* cell-free environment. Nor there is a guidance of the dosages and regimes that would enable PNAs to get across cell membranes under *in vivo* conditions and exert their effect on the complementary nucleic acids.

Contrary, Ganesh et al. (review reference, one of the authors of which, P. Nielsen, is applicant of this invention) teach that although peptide nucleic acids are known since beginning of 90-s (i.e., time of filing the priority application of this application),

> some, but surely not all, of the promises expected from this molecule has materialized. Most success, has been achieved within diagnostic use of PNA oligomers in hybridization and PCR. The development of PNA oligomers into gene therapeutic drugs is still in its infancy. (p. 931)

Ganesh et al acknowledge that progress in the use PNAs as therapeutic drugs - **in particular concerning cellular delivery** - has been made only within the past couple of years (and refers to publications of years 1999-2000).

The same is discussed in the Background Section of US 6,472,209 (i.e., the patent against which the interference is being provoked):

> The success of an oligonucleotide analog as an antigene or antisense agent requires that the oligonucleotide be taken up by cells in reasonable quantities such that the oligonucleotide reaches its target at a sufficient concentration. PNA oligomers, however, have low phospholipid membrane permeability (Wittung et al., FEBS Letters 365:27-29 (1995)) and have been reported to be taken up by cells very poorly (Hanvey et al., Science 258:1481-1485 (1992); Nielsen et al., Bioconjugate Chem. 5:3-7 (1994); Bonham et al., Nucleic Acids Res. 23:1197-1203 (1995); Gray et al., Biochem. Pharmacol. 48:1465-1476 (1997)), which would appear to limit their potential uses in antigene and antisense approaches.

In addition, Summerton (US 51420467), while acknowledging that nucleic acid analogs with uncharged backbones "have a potential" for enhanced rate of passage across cell membranes, expresses concern that

> There are, however, a variety of problems inherent in the structures of uncharged polynucleotide analogs of the type mentioned above. The structures are unstable in aqueous solution; do not allow assembly of different subunits in a defined order; and/or, the base-pairing moieties are not properly spaced for efficient binding to a target sequence. Further, molecular modeling studies carried out in support of the present invention indicate that in some structures the base-pairing moieties are linked too closely to the backbone to allow effective binding of the base-pairing moieties to contiguous bases of a complementary polynucleotide, while in other structures, there are excessive degrees of freedom for the base-pairing moieties, permitting undesired pairing of the moieties with noncomplementary (in the Watson/Crick sense) bases of a polynucleotide.

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art, one skilled in the art at the time the invention was made could not make and/or use the invention with the claimed breadth without an undue amount of experimentation. The skilled practitioner would first turn to the instant specification for guidance in practicing the full scope of the claimed method, however the specification only provides guidance to limited *in vitro* applications.. As such the practitioner would turn to the prior art for such guidance, however the prior art, at the time the invention was made, also lacked knowledge on how to produce *in vivo* effect on intracellular nucleic acid targets by extracellular administering PNAs. Finally, said practitioner would turn to trial and error experimentation to discover conditions of an *in* vivo administration without guidance from the specification or the prior art. Such represents undue experimentation.

Further, with respect to claims 38,43,53,61,70 drawn to "modification" of polypeptide expression, while specification provides support for inhibition of protein expression, it does not provide support for any other modification (e.g., stimulation) of polypeptide expression.

Response to arguments

Applicant discusses publication of Uhlmann et al, 1998. without addressing the merits of the publication, the reference is not considered because it is of post-filing date and enablement sufficiency of a specification is determined as of its filing date. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81 (Fed. Cir. 1986). See also MPEP 2164.05(a)

Further, applicant refers to publication of Hanvey et al cited in above discussed Uhlmann et al review. Examiner disagrees that microinjection addressed in Hanvey reads on in vivo treatment addressed in the instant claims. First, injection directly into nucleus of a cell can hardly be considered as "extracellular administration" addressed in the instant claims. Second, microinjection in general is not viewed as a method of *in vivo* administration.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. Claims 34-36,41,48-51,58,59,65-68 are rejected under 35 U.S.C. 102(e) as anticipated by Summerton et al (US 5,142,047)

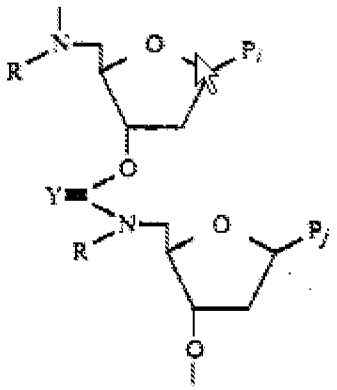
The instant claims are drawn to methods of treatment by *in vivo* administration of a polyamide nucleic acid oligomer containing neutral amide backbone linkages which is complementary to a target nucleic acid, under conditions wherein said oligomer engenders a biological response associated with said target. The claims specify that the administration is "extracellular". Claims 34-36,38-41,43-47 are directed to method of "treating living cells", whereas methods of claims 48-73 are directed to methods "comprising administering" said oligomer. Further, claims are directed to treating either cells, or mammals or organism (claims 34-36,38-40, claims 41-45,47, 58-64, and claims 65-73, respectively).

As the claims are directed either to extracellular administering *in vivo* or to treatment comprised of administering *in vivo*, it is Examiner's position that any reference teaching *in vivo* administration of oligomer as claimed will read on "extracellular administering *in vivo" or on "*treatment comprised of administering *in vivo*". As for the limitation "administering under conditions wherein said oligomer engenders a biological

response associated with said target", again, it is Examiner's position that any reference teaching *in vivo* administration of oligomer as claimed (i.e., oligomer which is complementary to a target nucleic acid) is read as administering under conditions wherein said oligomer engenders a biological response associated with target nucleic acid to which the applied oligomer is complementary.

As such the following reference is considered to read on the invention as claimed.

Summerton et al (US 5,142,047)[1] teach therapeutic administration of polymer composition effective to bind to a single-stranded polynucleotide containing a preselected target sequence of bases. See Abstract. The composition is composed of linked-subunit heteromeric polymer molecules, such as polymer comprised of subunits "B" and connected by amide backbone linkages. A part of the polymer structure, for two moieties "B", oligomer B-B, is exemplified in col. 5:



[1] Exemplary reference of multiple patents of the same applicant

wherein, for Y=O, the formula demonstrates an "oligomer containing neutral amide backbone linkage", and is a part of "polyamide nucleic acid oligomer" which contains "neutral amide backbone linkages".

The reference addresses use of the polymer composition for inhibiting biological activity of a single-stranded polynucleotide (col. 7, lines 45-47), disease-specific mRNA in particular (paragraph bridging columns 16-17). As the polymers of Summerton are binding compounds having desired binding activity to selected target sequence (col. 5, lines 1-7, and col. 16, bottom), and a target sequence is a single-stranded polynucleotide (col. 4, bottom), the oligomers of 5,142,047 read on oligomers administered as per the instant invention.

With respect to claims 35,49,66 directed to detecting biological response, as argued by applicant, disclosure of use to bind *in vivo* binding to target polynucleotides inherently teach monitoring the organism and detecting a biological response (response of 01/09/2008, p. 8, last full paragraph).

With respect to claims 51,59,68 specifying that the administered oligomer has sequence specificity to nucleic acid that regulates the expression or encodes a polypeptide, the reference teaches that the oligomers are complementary to single-stranded polynucleotides (col. 7, lines 45-47), disease-specific mRNA in particular (paragraph bridging columns 16-17) or genes (col. 17, line 53).

Response to arguments

Applicant points out that the compounds disclose in Summerton et al contain urethane, rather than amide, linkage. Examiner disagrees. The -O–CO-NR- linkage in

the reference is viewed as containing the neutral amide linkage (underlined) as instantly claimed.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-fre)e). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Borin/
Primary Examiner, Art Unit 1631